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Patent Foramen Ovale and Stroke: Prognosis and Treatment in Young Adults

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Abstract. **A patent foramen ovale (PFO) is found with increased frequency in patients with stroke of undetermined origin but the significance and therapeutic implications of this observation remain unclear. Several lines of evidence suggest a role for the PFO in stroke pathophysiology for some cryptogenic stroke patients, such as those whose PFO is accompanied by a prothrombotic state, atrial septal aneurysm, or lower extremity/pelvic DVT. Diagnostic evaluation of the patient with cryptogenic stroke and PFO is directed at identifying these subgroups. Appropriate therapy for primary and secondary stroke prevention in a subject with a PFO remains unclear given current uncertainties as to the pathophysiological significance of PFO. Additional studies are needed, such as those focused on lower extremity veins or the cardiac interatrial septum, to guide therapy in specific stroke subpopulations.**

Key Words. **cryptogenic stroke, stroke, patent foramen ovale, deep venous thrombosis, treatment**

Stroke is the leading cause of adult disability. Stroke is also the third leading source of mortality in the U.S., accounting for approximately 1 in 15 deaths [1]. There are over 730,000 new strokes diagnosed each year in the U.S. [2].

The young account for a significant fraction of these strokes. Though the median age of stroke in the U.S. is 72 years, approximately 28% of strokes occur in patients who are under age 65 [1]. In one U.S. study, 8% of all strokes occurred in patients between the ages of 20 and 45 [3]. In a large Japanese study, 7% of strokes occurred in patients age 16–50 [4]. This rate may be lower in European, and higher in developing, countries [5]. The one-month case fatality rate after ischemic stroke in patients <45 years of age is approximately half that of patients >45 [3]. Thus young stroke patients survive a long time, emphasizing the importance of secondary stroke prevention in this population.

There are many causes of stroke in general and this is equally true in younger stroke patients, where pathogenesis is often different from stroke in older patients [6]. Often no cause for stroke is apparent, in which case the stroke is termed cryptogenic.

The fraction of strokes that remains cryptogenic after careful evaluation is substantial and is increased in younger stroke patients. Across all patients with ischemic stroke, 30–40% are cryptogenic [7–12]. Studies suggest that this fraction is increased in younger patients. For example, one study found that the fraction of ischemic strokes that are cryptogenic in patients age 20–45 is 31% higher than in patients over 45 years [3]. In a study of patients <55 years of age, no cause for stroke was apparent in 64% of patients [13].

Cryptogenic stroke likely represents a number of different disease processes. Nevertheless, a large fraction of patients with a cryptogenic stroke share certain clinical features. Chief among these is an increased prevalence of a patent foramen ovale (PFO) [14].

Anatomic closure of the foramen ovale normally follows functional closure after birth, but a patent interatrial communication remains in a fraction of healthy subjects. One study found [15] that 6% of subjects had a PFO that was pencil patent (>5 mm diameter) and 29% of subjects had a PFO that was probe patent (2–5 mm). More recently, Hagen et al. [16] found that across all subjects at autopsy, 27.3% of subjects had a PFO, with mean diameter of 5 mm. Interestingly, this study also found that subjects <age 30 years had a higher prevalence of PFO, 34.3%, suggesting that the impact of any disease processes directly related to a PFO may be greater in younger patients. Echocardiographic studies have varied in their estimates of PFO prevalence among healthy subjects, but results are generally lower than values found in autopsy studies. This suggests that echocardiography has reduced sensitivity for identifying PFO as compared to anatomical inspection. The prevalence of PFO found in most echocardiography studies of healthy subjects has been between 10% [17] and 22% [18].

A PFO has been found to be present more often in patients with cryptogenic stroke than in patients with stroke of determined origin [13,17–27] or in healthy controls [13,17,18,21,28–30]. A PFO with concomitant atrial septal aneurysm is also found more often in patients with cryptogenic stroke, particularly younger patients [14]. The dual diagnosis of

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PFO and atrial septal aneurysm may have a particularly important association with stroke recurrence as vs. either diagnosis alone [31,32]. However, some authors have suggested that an atrial septal aneurysm may in part be a reflection of a larger PFO size [33].

Determination of PFO prevalence is made difficult by variability in the diagnostic sensitivity of current noninvasive methods. The sensitivity of transesophageal echocardiography (TEE) may be as much as two-fold greater than that of transthoracic echocardiography (TTE) for diagnosing a PFO [18,34], though addition of harmonic imaging using saline contrast can the sensitivity of TTE [35]. Transcranial Doppler (TCD) has sensitivity that approaches that of TEE [22,36,37], but decreased specificity. While TCD provides less information on cardiac structure as vs. echocardiography, it may be more sensitive to extracardiac right-to-left shunts. The choice of vein used to introduce echo contrast influences diagnostic sensitivity, as blood entering the right atrium via the inferior vena cava is more directed towards the interatrial septum region where a PFO is found, as compared to blood entering the right atrium via the superior vena cava. Thus, studies have found a 2.5-fold increase in diagnostic sensitivity for a PFO when agitated saline contrast was injected via the femoral vein rather than the antecubital vein [38,39].

The consistent observation that cryptogenic stroke is associated with an increased prevalence of PFO suggests the hypothesis that, in some of these patients, the PFO is a source or a conduit for thrombi that embolize to the brain. Other clinical characteristics commonly found in patients with cryptogenic stroke provide support for this hypothesis. First, the topography of cerebral infarct in patients with cryptogenic stroke and PFO is often suggestive of an embolic mechanism [7,26]. Second, several studies suggest that PFO size is greater in patients with cryptogenic stroke as compared to normal subjects or patients with stroke of determined origin [23,24,26–28,40,41]. However, PFO size is not related to risk of stroke recurrence [27,42]. Third, the prevalence of PFO patency at rest, i.e., without induction of a Valsalva-related pressure gradient, may be greater in patients with stroke as compared to control subjects [30].

A fourth line of evidence that in some patients may link PFO with pathophysiology of cryptogenic stroke is a significant prevalence of lower extremity deep venous thrombosis (DVT) in this patient population. Gautier et al. [43] performed venography 2 days to 7 months after cryptogenic TIA or stroke and found that 3/23 patients with PFO had leg DVT and 3 others had left common iliac vein compression. Ranoux et al. [25] performed venography within 4 weeks of cryptogenic stroke and found that 1/13 patients with PFO had a leg DVT. Lethen et al. [34] performed venography an average of 8 days after TIA or stroke of suspected cardiac origin and found that 5/53 patients with PFO had iliac or calf DVT. Stollberger et al. [44] found a leg or pelvic DVT in 19/29 patients with PFO and a cryptogenic arterial embolus, most of which affected the cerebral circulation. The prevalence of DVT was higher among patients studied within 1 week of embolus as compared to those studied 8–90 days post-event. Cramer et al. [45] found that 9/46 patients with cryptogenic stroke and PFO studied with MRI venography (MRV) an average of 2 days after stroke had evidence for a pelvic DVT.

There are a number of limitations in interpreting data linking DVT with PFO-related stroke. Most studies addressing this point have evaluated only a subset, rather than a consecutive cohort, of stroke patients. An additional limitation is that many studies have evaluated only part of the lower extremity venous system, or have used methods with limited sensitivity in portions of the lower extremity venous system. Another frequent limitation has been the absence of an appropriate control group, an important concern given the substantial increase in DVT prevalence that is found beginning with the fourth day post-stroke [46,47]. These observations might explain why reported rates of DVT have varied so widely in prior studies of patients with PFO and cryptogenic stroke.

Data on prothrombotic states bolster the link between DVT and cryptogenic stroke. Bendixen et al., in a study of 1,943 patients, concluded that prothrombotic states are a particularly important consideration in patients 15–35 years of age [6] Pezzini et al. [48] found that PFO played a pathogenic role in 36 of 125 young (mean age 35 years) patients with ischemic stroke. Among these 36, the prevalence of a prothrombotic genetic variant, particularly the prothrombin G20210A variant, was significantly increased as compared to patients in whom PFO was either absent or unrelated to stroke.

One issue that may be of particular importance in this regard is evaluation of calf veins. Isolated calf vein DVT is more common than DVT in any other site following stroke [46,49] and at autopsy [50] and so may be important before stroke, too. Proximal propagation may occur in 20–28% of calf vein DVT [51,52]. Embolization can occur without propagation, for example, an isolated calf DVT was found at autopsy in 36–46% of patients with PE [53]. Emboli from calf vein thrombi tend to be small and asymptomatic on reaching the lung [54,55], and in general medical practice, little emphasis is placed on treatment of calf vein DVT when extension to popliteal veins does not occur [56]. However, an embolus from a calf vein might be of substantially greater clinical significance upon reaching the cerebral circulation [57], and the incidence of paradoxical embolism in patients with acute pulmonary embolism has been estimated to be as high as 60% [58]. DVT from calf veins may not be rare and, while of little significance to the lungs,

can cause serious brain injury upon reaching the arterial circulation. A recent case series described several cryptogenic stroke patients with a calf vein DVT and PFO in whom the calf DVT was established as the cause of stroke on a probable basis [59].

Study of the pelvic veins may also be important in the context of PFO-related stroke. In autopsy studies of patients with a paradoxical embolism, the pelvic veins were the only source of thromboemboli in 22% of patients [60,61]. A consecutive study of 769 MRI venograms [62] found that 20% of the 167 DVT identified were isolated to the pelvic veins. Pelvic DVT have been described in patients with cryptogenic pulmonary embolism [63–65] and in patients with cryptogenic stroke with PFO [59,66–68].

The Paradoxical Embolism from Large Veins in Ischemic Stroke (PELVIS) study [45] performed a pelvic MRV within 72 hours of stroke onset in young (18–60 year-old) consecutive stroke patients at five U.S. academic centers. Testing to identify the cause of stroke was subsequently performed during hospitalization. This study was designed to test the hypothesis that patients with cryptogenic stroke have an increased prevalence of pelvic DVT as compared to patients with stroke of determined origin. This time cutoff of 72 hours was selected to minimize the influence of DVT arising after stroke onset. The age cutoff was selected to focus on young stroke patients, in whom the link between PFO and cryptogenic stroke is strongest [14]. Enrolled patients were mean age 46 years. The PELVIS study found that, compared to those with stroke of determined origin ($n = 49$), patients with cryptogenic stroke ($n = 46$) were significantly younger, had a higher prevalence of PFO (61% versus 19%), and had less atherosclerosis risk factors. Most importantly, cryptogenic patients had more MRV scans with a high probability for pelvic DVT (20%) than patients with stroke of determined origin (4%, $P < 0.03$), with most of these having an appearance of a chronic DVT. The most commonly involved vein was the external iliac vein, followed by common iliac vein, consistent with a prior report of pelvic DVT distribution [62]. A limitation of this study was that inter-rater reliability for MRV interpretation was not high.

Further studies are needed to understand the significance of calf, pelvic, and other DVT in the pathogenesis of PFO-associated cryptogenic stroke. Lower extremity venous duplex does not include study of calf veins in some institutions, but identification of such small DVT might be necessary in the context of cryptogenic stroke. Imaging the pelvic veins has traditionally been limited. Bilateral contrast venography and other diagnostic methods have reduced diagnostic sensitivity for pelvic DVT [47,69,70]. MRI venography was of diagnostic value in the PELVIS study [45], but inter-rater reliability was not high. A number of investigators are currently examining improved methods to image lower extremity/pelvic veins, including gadolinium-enhanced MR venography [71], MR direct thrombus imaging [72], venous enhanced subtracted peak arterial MRV [73], CT venography [63,64], and signal-enhanced Doppler [74].

Even as the pathophysiology of cryptogenic stroke continues to be studied, clinicians have recognized that medical therapy in patients with a cryptogenic stroke may be associated with an important stroke recurrence rate, the precise extent of which remains unclear. In patients with cryptogenic stroke/TIA, reported annual rates of recurrence have included 16% [75], 5.4% [30], 3.4% [76], and 3.8% (84% were cryptogenic in this study) [77], Mas et al. [31] found a stroke recurrence rate of 1% when both PFO and atrial septal aneurysm were absent vs. 3.8% when both were present. A recent large, prospective study found that the combined annual rate of death or recurrent ischemic stroke among patients with cryptogenic stroke was 7.8% [9], though a substudy found that the annual rate of death/recurrent stroke after a cryptogenic stroke was not significantly different when PFO was (7.2%) or was not (6.4%) present [27]. A recent meta-analysis concluded that "PFO is not associated with increased risk of subsequent stroke or death among medically treated patients with cryptogenic stroke. However, both PFO and ASA possibly increase the risk of subsequent stroke (but not death) in medically treated patients younger than 55 years." [32]. Future studies might examine the hypothesis that specific subgroups of patients with PFO and stroke can be identified in whom the risk of stroke recurrence is increased [78].

There are several therapeutic options available for primary and secondary stroke prevention in a person with a confirmed PFO, including antiplatelet agents, anticoagulation, and closure of the PFO via either a transcatheter or surgical approach. The risk-to-benefit ratio among these choices, however, remains unclear [79].

Complicating therapeutic decision-making in this context is the fact that, in most patients, no clear understanding of the role of a PFO in stroke pathogenesis is present. A PFO is not in itself a pathological finding—the 27–29% [15,16] prevalence of this cardiological variant in healthy people indicates current existence of nearly two billion PFOs worldwide. Treatment of PFO will be best directed when a physician is able to understand the pathophysiological events being targeted, and these events require further study. While considerable evidence correlates presence of PFO with occurrence of cryptogenic stroke, especially in younger patients, this link could reflect several different possibilities across the broad patient population. For example, the link could reflect a second, co-linked pathophysiology that results in stroke such as atrial arrhythmias [80] or other cardiac electrophysiological changes [81], it could indicate PFO as the site of cardiac embolism

formation, or it could reflect PFO as a conduit for passage of paradoxical embolism. It is not surprising that for some stroke subpopulations, recurrence of ischemic brain events has been found not to be rare despite complete PFO closure [82].

In the absence of a clear pathophysiological understanding, therefore, treatment of PFO-related stroke remains controversial. Some experts recommend that secondary stroke prevention in a patient with a cryptogenic stroke, with or without PFO, is generally achieved with an antiplatelet agent [83]. Retrospective data suggest that coumadin is superior to antiplatelet therapy [84]. Consistent with this, one model suggests that if the estimated risk of paradoxical stroke recurrence is $>0.8\%$ per year, secondary stroke prevention should be achieved with either anticoagulation or PFO closure [85]. Our practice has been that, until prospectively collected data support widespread use of anticoagulation in patients with PFO and ischemic stroke, coumadin is indicated only in patients with an appropriate therapeutic target. Examples include a prothrombotic state or ischemic stroke arising from a DVT passing through a PFO as a paradoxical embolism on a probable basis. We have defined 'probable basis' [59] as diagnosis of a DVT less than 4 days [46] after stroke onset in the presence of either PFO or atrial septal defect.

The role of PFO closure for primary or secondary stroke prevention also remains unclear. There are currently limited data directly comparing closure with best medical therapy in patients with stroke, and this question is currently being evaluated in prospective controlled trials [86]. PFO closure may be especially efficacious in specific patient subpopulations. Corollary investigations might therefore attempt to define such subpopulations, for example, on the basis of prothrombotic state, migraine status, measures of brain white matter injury, features of cardiac interatrial anatomy, or electrophysiological cardiac assessments. Recommendations [87] that certain features of history should prompt PFO closure would be of increased value if studied in prospective controlled trials.

Diagnostic evaluation of a patient with cryptogenic stroke and PFO currently attempts to identify abnormalities that would best direct therapy. Identification of a DVT, especially less than four days [46] after stroke onset, suggests paradoxical thromboembolism and a need for anticoagulation. We therefore try to study calf, popliteal, femoral, and pelvic veins when possible. Identification of a prothrombotic state might also suggest anticoagulation, and so hematological evaluation for both venous and artieral hypercoagulabile states is performed. Some authors recommend transesophageal echocardiogram for measurement of PFO and/or interatrial septum size to guide the decision for PFO closure [87].

PFO is common in healthy human subjects. The frequency of PFO is increased among patients with a cryptogenic stroke. Several lines of evidence suggest a role for the PFO in stroke pathophysiology for some patients, particularly those with a concomitant prothrombotic state, atrial septal aneurysm, or lower extremity/pelvic DVT. New treatments to safely close PFO are under evaluation [86,87]. A method to identify patients most likely to achieve long-term benefit from this intervention remains to be established. In this regard, a paradigmatic shift in thinking about small lower extremity DVT may be needed to understand stroke pathogenesis in patients with cryptogenic stroke, as emboli of no significance to the lung could, upon reaching the arterial circulation, cause substantial brain ischemia and disability. Preventing TIA, stroke, and death after a diagnosis of cryptogenic stroke may be best guided by a better a more precise understanding of the various pathophysiologies underlying PFO-associated cryptogenic stroke. In the absence of such data, divergent therapeutic strategies have been recommended [83,85,87].

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